ORIGINAL ARTICLE

RESULTS OF SURGERY IN LUNG CANCER– A RETROSPECTIVE STUDY OF A SINGLE CENTER EXPERIENCE

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Abstract

Objectives: *Surgery provides the best chance for cure in patients with non-small-cell lung cancer stage I or II, but only a small portion of all new cases diagnosed are eventually suitable for surgical resection. Our goal was to appraise the surgical outcomes including survival and progression rates in patientswith histological diagnosis of lung cancer.*

Methods: *Between 1st August 2012 and 30th June 2018, the patients with histological lung cancer diagnosis that underwent surgical resection with a curative intent at the department of Cardiothoracic Surgery of Centro Hospitalar Universitário de São João were included.*

Results: *The majority of patients were pathological stage I and the most performed surgery was a lobectomy (90.6%). The hospitality mortality was 1,3% and the rate of complication was 26,1%. Patients with forced expiratory volume in 1 second (FEV1) less than 80% had higher (statistically significant difference) frequency of complications. Active smokers, Eastern Co-operative Oncology Group Performance Status (ECOG PS)value different than 0 and FEV1 inferior to 80% had a higher mean length of drainage and higher mean length of stay (statistically significant difference). The overall survival was 92,6% at 1 year, 87,7 % in 2 years and 79,1% in 5 years. The overall survival according to pathological stages were similar when compared with the literature.*

Conclusions: *Ours results are similar to international centers and we should be more alert to preoperative assessment.*

Keywords: *Lung Cancer; Lobectomy; Overall Survival; Thoracic Surgery.*

INTRODUCTION

Lung cancer is the leading cause of cancer-related mortality around the world. Approximately 85% of lung cancers diagnosed annually worldwide are non-small cell lung cancer (NSCLC). Surgery remains the best treatment option but close to 70% of patients with lung cancer present with locally advanced or metastatic disease at the time of diagnosis, so only 30% of all diagnosis are eventually suitable for surgical resection with a curative intent[1,2].

According to Goldstraw et al[3] the 5-year overall survival ranges between 90% for pathologic stage IA1 and 41% for stage IIIA for surgical patients with NSCLC.

Our goal was to appraise our surgical outcomes including survival and progression rates.

Patients and Methods

Between 1st August 2012 and 30th June 2018, the patients with histological lung cancer diagnosis that underwent surgical resection with a curative intent at the department of Cardiothoracic Surgery of Centro Hospitalar Universitário de São João (CHUSJ) were included. We excluded patients with incomplete surgical resection (microscopic or macroscopic residual tumor).

Population was characterized by demography and clinical variables and surgical results were displayed. De-

Table 1 **Demography data and Clinical Presentation**

Thoracic Surgery	n= 310	
Sex	n (%)	
Male	196 (63,2)	
Female	114 (36,8%)	
Tobacco	n (%)	
Active smoking	103 (33,2%)	
Former smoking	101 (32,6 %)	
Non-smoking	106 (34,2%)	
ECOG PS	n (%)	
0	209 (67,4%)	
1	100 (32,3%)	
2	1 (0,3%)	
	Median (min-max)	
FEV1	96 (29,4-160)	
DLCO	82 (20-136)	
Comorbidities	n (%)	
CRF (tobacco excluded)	217 (70,0%)	
CVD	48 (15,5%)	
CKD	14 (4,5%)	
COPD	41 (13,2%)	
Asthma	8 (2,6%)	
Interstitial lung disease	7 (2,3%)	
Tuberculosis sequelae	14 (4,5%)	
Prior Neoplasms	76 (24,5%)	
Tumor Location	n (%)	
Central	78 (25,2%)	
Peripheric	232 (74,8%)	
Surgical Intervention	Total Cases (%)	VATS (n) » 6.8%
Lobectomy	281 (90,6%)	17 (5,5%)
Right	156 (50,3%)	12 (3,9%)
» Superior	75 (24,2%)	5 (1,6%)
» Middle	21 (6,8%)	0*
» Inferior	60 (19,6)	7 (2,3%)
Left	125 (40,3%)	5 (1,6%)
» Superior	73 (23,5%)	3(1,0%)
» Inferior	52 (16,8%)	2(0,6%)
Bilobectomy	9 (2,9%)	1 (0,3)
Superior	3 (1,0)	1 (0,3)
Inferior	6 (1,9)	0
Pneumectomy	9 (2,9%)	0
Right	5 (1,6%)	0
Left	4 (1,3%)	0
Sublobar Resection	5 (1,6%)	3 (1,0%)
Lobectomy + Sublobar Resection	6 (1,9%)	0
Histology	n (%)	
Adenocarcinoma	222 (71,6%)	
Neuroendocrine	52 (16,8%)	
Squamous	28 (9,0%)	
Mixed	8 (2,6%)	
» Adenocarcinoma	4 (1,3%)	
+ Squamous		
» Adenocarcinoma	3 (1,0%)	
+Neuroendocrine		
» Adenocarcinoma	1(0,3%)	
+ Small Cell Lung Cancer		
Pathological Stage	n (%)	
IA	131 (42,3%)	
IB	100 (32,3%)	
IIA	7 (2,3%)	
IIB	50 (16,1%)	
IIIA	20 (6,5%)	
IIIB	2 (0,6%)	
First-line treatment	n (%)	
Surgery	172 (55,5%)	
Surgery + CTX	108 (34,8%)	

Surgery + CTX +RT	17 (5,5%)	
Neoadjuvant CTX and RT + Surgery	2 (0,6%)	
Neoadjuvant CTX+ Surgery +CTX +RT	3 (1,0%)	
Neoadjuvant CTX +Surgery	3 (1,0%)	
Neoadjuvant CTX + Surgery +CTX	5 (1,6%)	
	Median (min-max)	
LOD (days)	5 (1-39)	
LOS (days)	6 (1-49)	
Complications	n (%)	
PAL	39 (12,6%)	
AF	19 (6,1%)	
NRI	14 (4,5%)	
Persistent Serous Drainage	7 (2,3%)	
Chylothorax	4 (1,3%)	
ARF	6 (1,9%)	
Paralytic Ileus	2 (0,6%)	
Vocal Cord Paralysis	1 (0,3%)	
Acute Pulmonary Edema	2 (0,6%)	
Hospital Mortality	4 (1,3%)	
Hemorrhagic shock	1 (0,3%)	
BPF	1 (0,3%)	
Pulmonary Torsion	1 (0,3%)	
Septic shock	1 (0,3%)	

Min-minimum; Max-Maximum;ECOG PS-Eastern Cooperative Oncology Group-Performance Status; CRF- Cardiovascular Risk Factors,CVD-Cardiovascular Disease; CKD-Chronic Kidney Failure; COPD-Chronic Obstructive Pulmonary Disease; FEV1-Forced Expiratory Volume in 1 Second; DLCO- Diffusing Capacity for Carbon Monoxide; VATS-Video-Assisted Thoracoscopic Surgery; CTX – Chemotherapy; RT-Radiotherapy; LOD-Length of Drainage; LOS-Length of Stay; PAL-Persistent Air Leak; AF-Atrial Fibrillation; NRI- Nosocomial Respiratory Infection; ARF- Acute Renal Failure; BFC- Bronchopleural Fistula.
**One middle lobectomy started VATS but was converted.*

scriptive analysis was performed and data presented as counts and proportions for categorical variables. Measures of central tendency and dispersion were appliedfor continuous variables, according to their distribution. Results were considered statistically significant if $p < 0,05$.

Survivals were estimated based on the Kaplan-Meier method and their comparison of survival curves, performed using the log-rank test. Chi-square test and independent t-test were applied respectively for categorical and continuous variable.

RESULTS

In this period 319 patients with lung cancer were submitted to thoracic surgery with a curative intent, but we excluded 9 patients with incomplete surgical resection (microscopic or macroscopic residual tumor). Time for surgery was defined as the difference between surgery date and date of histological diagnosis (median = 74 days). We considered ex-smokers if the patient smoked more than 100 cigarettes in their lifetime and if has not smoked at least in the last 12 months at the time of diagnosis. We used this definition because of risk of relapse in patients that recently quit smoking.The presence of hypertension, diabetes mellitus or/and dyslipidemia was recorded as cardiovascular risk factors (CRF). We used the 8th TNM (tumor, node and metastasis) classification for lung cancer and all the pathological stages were updated.

Survival and progression rates

The progression was defined as imagological progression and it was defined as the difference between local or distant progression date and the date of histological diagnose. Tumor recurrence anywhere within ipsilateral hemithorax was considered local progression and recurrence with extrathoracic involvement was distant progression. Global progression frequency was 19,4% (60). The mean time of progression was 21months (1-73months).

The progression free survival (PFS) was 92,3 % at 1 year, 86,7% in 2 years and 77,7% in 5 years to all surgical stages. The local PFS was 94,9% at 1 year, 89,9% in 2 years and 84,1% in 5 years to all surgical stages. The distant PFS was 95,0% at 1 year, 91,6% in 2 years and 84,1% in 5 years to all surgical stages. The overall survival (OS) was 92,6% at 1 year, 87,7 % in 2 years and 79,1% in 5 years. The PFS (Table 2) and OS (Table 3) according to pathological stages (Table 2) were displayed and the resulting p value for the log rank test was 0,002 and 0,019 respectively.

There was a statistically significant difference between having a complication and a forced expiratory volume in 1 second (FEV1)inferior to 80% vs having a complication and FEV1 equal or higher than 80% (Chi-square test $p < 0,001$). There was no statistically significant difference between having a complication and being active smoker vs having a complication and being former or non-smoker ($p=0,456$); having a complication and Eastern Cooperative Oncology Group Performance Status (ECOG PS) value different than 0 vs having a complication and ECOG PS value equal to 0 ($p=0,087$); having a complication and CRF vs having a complication and no CRF ($p=0,331$) having a complication and central tumor vs having a complication and a peripheric tumor location ($p=0,289$).

There was no statistically significant difference between having persistent air leak (PAL) and being active smoker vs having PAL and being former or non-smoker (Chi-square test $p=0,397$).

Table 2 **Progression Free Survival according to pathological stages**

	Stage	IA	IB	IIA*	IIB	IIIA*	IIIB*
PFS (%)	1year	95,2	94,7	85,7	81,4	51,8	50,0
	2years	93,6	89,0	85,7	72,4	38,8	50,0
	5years	92,5	83,2	85,7	58,3	38,8	50,0

PFS: progression Free Survival
** The number of patients in these stages were low in comparison with other surgical stages.*

Table 3 **Overall Survival according to pathological stages**

	Stage	IA	IB	IIA*	IIB	IIIA*	IIIB*
OS (%)	1year	93,1	91,0	100	83,8	80,0	100,0
	2years	91,4	88,6	100	76,1	75,0	50,0
	5years	83,6	82,9	100	53,5	75,0	50,0

OS: Overall Survival
** The number of patients in these stages were low in comparison with other surgical stages.*

DISCUSSION

The primary risk factor for lung cancer is smoking tobacco, which accounts for most lung cancer-related deaths[4]. According National Health Committee in Portugal the prevalence of smokers was twice higher in men than in women in 2015[5] and this could be an explanation why 63,2% of our patients were male.

A good performance status (ECOG 0 or 1) is a good prognostic factor of survival in patients with NSCLC[4], but in a population submitted to surgery is also used for assessing patient fitness to surgery, as also values of FEV1 anddiffusing capacity for carbon monoxide(DLCO). In our study only one patient had an ECOG = 2, and this patient with 72-years-old was submitted to a sublobar resection and the pathological findings reveal a typical carcinoid. Lobectomy remains the standard for surgical management of NSCLC although sublobar resection for NSCLC is still a controversial issue[1,6]. Rami-Porta and Tsuboi(6) reported in terms of survival, lobectomy and wedge resection are equivalent in patients aged more than 71 years and in patients unable to undergo lobectomy, sublobar resection is an alternative that will confer similar prognosis.

The patient with the lowest FEV1 and DLCO (29,4 % and 20,0 % respectively) was submitted to middle lobectomy and pathological findings reveal a pT2a N0 R0 adenocarcinoma. This patient was an active smoker with a chronic obstructive pulmonary disease (COPD) diagnosed and chylothorax was the only complication described. We do not have any information about a more extensive assessment through pulmonary exercise testing but computed tomography (CT) of the chest showed paraseptal emphysema mainly in upper and middle lobes.The distant progression occurs after 28 months and he died 30,5 months after diagnosis of NSCLC.

In Portugal we don't have a lung cancer screening program so the majority of patients did a CT scan because a prior neoplasm (in our study the second more frequent comorbidity was a prior history of other neoplasm), a chest trauma or unspecific respiratory symptoms.

The majority of tumours were peripheric (peripheral to the subsegmental bronchi) which is concordant with the predominant histology type (adenocarcinoma).

Table 4 **Differences between length of drainage and length of stay and respectively p values**

	LOD (mean; days)	p value (independent t-test)	LOS (mean; days)	p value (independent t-test)
Active smoker	7.5	0.013	9.1	0.026
Former or Non-smoker	6.4		7.7	
ECOG PS =0	6.3	0.008	7.5	0.003
ECOG PS ≠0	7.8		9.7	
FEV1 <80	8.2	≤0.001	10.0	≤0.001
FEV1 ≥80	6.4		7.7	
CRF	7.0	0.266	8.4	0.324
No CRF	6.2		7.6	
Central location	6.8	0.244	8.6	0.411
Peripheric location	6.8		8.0	

LOD-Length of Drainage
LOS- Length of Stay
ECOG PS-Eastern Cooperative Oncology Group Performance Status
FEV1-Forced Expiratory Volume in 1 Second;
CRF- Cardiovascular Risk Factors

Lobectomy was the surgery most performed, especially the upper lobes lobectomy which is explained by predilection of lung cancer for the upper lobes.

We started our program of video-assisted thoracic surgery (VATS) in June 2017 and that's the reason why only 6.8% of the surgery were VATS. Nowadays the majority of lobectomies performed at our department are VATS. VATS is a less invasive procedure and it is associated with a lower incidence of complications, lower length of stay (LOS) and same oncologic results when compared with thoracotomy [7]. We believe that the length of drainage (LOD) and LOS presented in this study could be lower if the lobectomies were performed by VATS.

Surgery provides the best chance for cure in patients with stage I or II disease, and most of our patients were this pathological stage. Although surgery for stage IIIA is still controversial[4], the two patients stage IIIB submitted to thoracic surgery were upstaged atpathologic staging as the majority of IIIA stage. We presented more patients submitted to surgery with a pathological stage IIB that stage IIA and that could be a selection bias.

Allen et al[8] reported that lobectomy had an operative mortality (within the first 30 days after surgery or during the same hospitalization) of 1,3% and that is exactly our hospitality mortality rate. They analyse 1023 patients and reported one or more complications occurred in 38,0 % of patient, and atrial arrhythmia (AF) was the most prevalent complication (14,3%). Our study had a lower rate of complications (26,1%) and AF only appears in second place but we reported a higher frequency of PAL (12,6% vs 7,6%). Some surgeons will not operate on a current smoker, because active smoking may increase postoperative pulmonary complications[9]. For this reason, we looked for association between PAL and being active smoking, having a complication and being active smoking but no statistically significant difference was found in our study. However, the active smokers had a higher mean LOD and higher mean LOS (statistically significant difference). ECOG value different than 0 also had a higher mean LOD and higher mean LOS (statistically significant difference), but because of this subgroup is less independent we can extrapolate that they have probably longer postoperative immobility time.

There was a statistic significant difference in mean LOD; mean LOS; having a complication and having a FEV1 value less than 80%. This cut-off is used in preoperative respiratory evaluation to resection up to pneumonectomy[10].

PFS and OS are two common endpoints in cancer trials, but increase in PFS does not necessarily result in an increase in OS. OS is usually preferred, because it is reliable, precise, meaningful, and can easily be documented[11]. In our study PFS and OS to all surgical stages are very similar but this does not happen with PFS and OS according to pathological stage. The number of patients in stages IIA, IIIA and IIIB were very low in comparison with other pathological stages which does not allow correct interpretation in comparison with other stages: for example, the 2 patients stage IIIB were alive after 1 year, so the OS was 100% for stage IIIB but only 93,1% for stage IA.

Comparing our results with Goldstraw et al[3], the 2-years OS ranges between 97% (IA1), 94% (IA2) and 92% (IA3) and our results for the stage IA was 91.4%. The 5-years OS ranges between 90% (IA1), 85% (IA2) and 80% (IA3) and ours results for the stage IA was 83,6%. There was no statistically significant difference between our results and the literature results (p =0,553 and p=0,929 respectively).

Goldstraw et al reported the 2-years OS of 89% for stage IB and our results showed 88,6% at this pathological stage (p= 0,998). There was a statistically significant difference between their 5-years OS (73%) and our 5-years OS (82,9%) for stage IB p=0,025)

The results of pathological stage IIB was very similar: 2-years OS (76% vs 76,1% p=0,999); 5- years OS (56% vs 53,5% p=0,776). The similar results, although the huge different between the numbers of patients reported for Goldstraw et al and our 310 patients makes us believed that our results would be very close in all stages if the number of patients was similar.

CONCLUSION

These results have implications for daily clinical practice since they reaffirmed that our results are similar to international centers and make us more alert to preoperative assessment particularly to ECOG PS Scale, the value of FEV1 (and not only calculated the predicted postoperative value) and smoking cessation.

REFERENCES

1. Molina JR, Yang P, Cassivi SD, Schild SE, Adjei AA. Non-small cell lung cancer: epidemiology, risk factors, treatment, and survivorship.. Mayo Clin Proc. 2008;83(5):584-594. doi:10.4065/83.5.584
2. Le Chevalier T. Adjuvant chemotherapy for resectable non-small cell lung cancer: where is it going? Ann Oncol. 2010;21Suppl 7:vii196-vii198. doi:10.1093/annonc/mdq376
3. Goldstraw P, Chansky K, Crowley J, Rami-Porta R, Asamura H, Eberhardt WE et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the stage grouping in the forthcoming (8th) edition of the TNM classification of lung cancer. J ThoracOncol. 2016;11(1):39-51. doi:10.1016/j.jtho.2015.09.009
4. National Comprehensive Cancer Network. Guidelines Non-Small Cell Lung Cancer. Version 4.2021.
5. Direcção Nacional de Saude, Relatório do Programa Nacional para a Prevenção e Controlo do Tabagismo 2019
6. Rami-Porta R, Tsuboi M. Sublobar resection for lungcancer. EurRespir J. 2009;33(2):426-435. doi:10.1183/09031936.00099808
7. Falcoz PE, Puyraveau M, Thomas PA, Decaluwe H, Hürtgen M, Petersen RH et al. Video-assisted thoracoscopic surgery versus open lobectomy for primary non-small-cell lung cancer: a propensity-matched analysis of outcome from the European Society of Thoracic Surgeon database. Eur J Cardiothorac Surg. 2016;49(2):602-609. doi:10.1093/ejcts/ezv154
8. Allen MS, Darling GE, Pechet TT, Mitchell JD, Herndon JE 2nd, Landreneau RJ et al. Morbidity and mortality of major pulmonary resections in patients with early-stage lung cancer: initial results of the randomized, prospective ACOSOG Z0030 trial Ann Thorac Surg. 2006;81(3):1013-1020. doi:10.1016/j.athoracsur.2005.06.066
9. Marino KA, Little MA, Bursac Z, Sullivan JL, Klesges R, Weksler B. Operating on Patients Who Smoke: A Survey of Thoracic Surgeons in the United States. Ann Thorac Surg. 2016;102(3):911-916. doi:10.1016/j.athoracsur.2016.03.076
10. P. E. Postmus, K. M. Kerr, M. Oudkerk, S. Senan, D. A. Waller, J. Vansteenkiste et al. Early-Stage and Locally Advanced (non-metastatic) Non-Small-Cell Lung Cancer: ESMO Clinical Practice Guidelines. Ann Oncol. 2010;21Suppl 5:v103-v115. doi:10.1093/annonc/mdq207
11. Imai H, Kaira K, Minato K. Clinical significance of post-progression survival in lung cancer. Thorac Cancer. 2017;8(5):379-386. doi:10.1111/1759-7714.12463